Medical and Pediatric Oncology 26:261–263 (1996)

RSV Infection Complicating the Therapy of Pediatric Malignancies: Report of Six Cases

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We describe a series of six patients with symptomatic respiratory syncytial virus (RSV) infections while receiving anticancer chemotherapy. Particularly during epidemics in the general population, RSV remains a potential cause for morbidity and even mortality among children immunocompromised through the administration of anticancer chemotherapy and especially those being transplanted. We emphasize the importance of rapid diagnostics as well as prevention of the spread of the virus in a pediatric hematology/oncology unit.

Key words: respiratory syncytial virus, children, immunosuppressed

INTRODUCTION

Respiratory syncytial virus (RSV) is a potential cause of serious morbidity and even mortality among children and adults receiving anticancer chemotherapy or a bone marrow transplantation [1–4]. Reports on RSV infections among pediatric oncologic patients are few. In their series of 47 immunocompromised pediatric patients with RSV infection, Hall et al. [2] included 20 on chemotherapy for a malignant disorder. All of these 20 patients had pneumonia, a prolonged viral shedding (up to 6–7 wk) and were faced with a 15% mortality. More than 50% acquired for their infection nosocomially. Upon admission for RSV, all were lymphopenic and ~ two-thirds were neutropenic with an absolute neutrophil count (ANC) below 900×10^6/l. A minority of their patients had a relapse in their shedding of the virus as well as pneumonia with recurrent neutropenia. Navas and coworkers [5] did not specify the number of oncologic patients in their series of 35 immunocompromised children. They reported substantial RSV related morbidity but no mortality.

Ribavirin is a nucleoside analog with good in vitro activity against RSV, and no clinical resistance has thus far been observed [6]. The use and benefit of aerosolized ribavirin in the treatment of severely symptomatic immunocompromised adult patients have been fairly well established [1,3,4], but pediatric data on the subject are scanty. The role of intravenous ribavirin in this setting remains unresolved.

We describe a series of cases with symptomatic RSV infections among children receiving anticancer chemotherapy in order to shed additional light on the course, treatment, and outcome of RSV infections among children with cancer.

MATERIALS AND METHODS

Immunofluorescence microscopy was employed to detect RSV antigen in nasopharyngeal secretion [7]. RSV antibodies were examined using complement fixation. Cultures for RSV were performed using the human amnion and green monkey kidney cell lines.

Patients

Finland went through a nationwide epidemic of RSV between mid-September 1993 and the end of January 1994. As a part of this epidemic, a series of cases with mild to severe RSV infections were encountered among the patients of our pediatric oncology unit. A total of six patients (ages 13–52 mo, mean 24 mo) were affected. For a summary of their essential RSV-related clinical details, see Table I. The case histories of patients 1 and 5 are detailed below.

All of the patients were receiving intensive chemotherapy at the time of their RSV infection, three for neuroblastoma (NBL) and three for acute lymphoblastic leukemia (ALL). One of the NBL patients had started an autologous bone marrow transplantation (BMT) program

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Received November 22, 1994; accepted February 20, 1995.

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TABLE I. Patient Summary

No.	Age (mos)	M/F	Dg.	Ongoing therapy	ANC[a] & Lymph. <500[b]	Ribavirin inh.	Ribavirin iv	RSV antibodies[c]	RSV viral culture	RSV antigen positivity[d] (wks)	Outcome
1	15	F	NBL[e]	aBMT[f]	−/+	+	+	ND	+	>2	Died
2	22	M	ALL[g]	Primary induction	+/+	+	−	ND	−	3	Recovered
3	22	M	NBL	Conventional chemotherapy	−/−	−	−	−	−	2	Recovered
4	52	F	ALL	Primary induction	+/+	+	+	−	−	6	Recovered
5	13	F	ALL	Primary induction	+/+	+	+	+	−	4	Recovered
6	22	F	NBL	Conventional chemotherapy	−/−	−	−	−	−	1	Recovered

[a]Absolute neutrophil count.
[b]ANC & lymphocytes $<500 \times 10^6$/l at diagnosis of RSV infection/during infection.
[c]Diagnostic seroconversion.
[d]Total duration of positivity in weekly to bi-weekly samples.
[e]Neuroblastoma.
[f]Autologous bone marrow transplantation.
[g]Acute lymphoblastic leukemia.
ND = not determined.

when a symptomatic RSV infection was detected. While having a clinical RSV infection, all of our patients concurrently received broad spectrum antibacterial treatment mostly with imipenem-cilastatin. However, none of the patients had a documented infection caused by an organism other than RSV. None of the patients received gamma globulin.

In all of the patients, the diagnosis of an RSV infection was based on the clinical signs together with the presence of RSV antigen in the nasopharyngeal secretion. Only one of the patients (case 5) demonstrated a diagnostic increase in RSV antibodies. RSV was successfully cultured from the pharyngeal secretions of only the most severe of our cases (case 1).

The clinical course of the RSV infection involved upper respiratory tract symptoms followed by pneumonia. However, only the one with a fatal outcome was in the need of supplementary oxygen as well as ventilatory assistance. Except for Case 5 (see below), none of the patients had signs of extrapulmonary involvement of RSV. All of those who recovered did so within 3–4 weeks from the diagnosis of their RSV infection.

Four of the six patients received inhaled and three of the six received intravenous ribavirin. Aerosolized ribavirin was administered using a SPAG-2 (small particle aerosol generator, Viratek, Costa Mesa, CA) device into a tent with a dose of 4 g/12–18 hours/day on 3 consecutive days. Intravenous ribavirin was administered with a dose of 20 mg/kg/day for 4–6 days. Apart from mild respiratory irritation related to the administration of aerosolized ribavirin, no adverse reactions or toxicity were encountered.

In all the patients who were neutropenic but eventually recovered from their RSV infection, the resolution of clinical symptoms as well as the cessation of viral shedding coincided with marrow recovery, and none of the patients experienced an RSV relapse with recurrent neutropenia.

CASE REPORTS

Case 1

A 15-month-old girl was diagnosed with stage IV neuroblastoma in April 1993. Upon admission for autologous BMT in November, she had only mild upper respiratory tract symptoms. Only after the commencement of her BMT program was she discovered to be RSV positive through the results of both culture and antigen detection and remained so throughout the rest of her illness. Shortly posttransplant, she became feverish and her respiratory signs progressed to a bilateral pneumonia with atelectasis. She received a 3-day course of inhaled ribavirin, but it failed to stop the progression of the respiratory problems. While granulo/lymphopenic and with a progressing bilateral pneumonia, she developed a need for supplementary oxygen first administered through continuous positive airway pressure and then through a respirator. Thereafter she remained ventilator-dependent with decreasing respiratory capacity. Iv ribavirin was also administered for 4 days. She demonstrated marrow engraftment on day +7 post-BMT and reached an ANC of $\sim 300 \times 10^6$/l on day +10, when she died of respiratory failure. Autopsy revealed an extensive, bilateral RSV pneumonia with multinucleated giant cells.

Case 5

A 13-month-old girl was diagnosed with ALL in December 1993. While granulo/lymphopenic and receiving standard induction chemotherapy, she developed signs of respiratory distress and a bilateral pneumonia with atelectasis as well as seizures and other clinical signs consistent with encephalitis and a highly but nonspecifically abnormal EEG. She was positive for RSV antigen in the nasopharyngeal samples and demonstrated a diagnostic increase in anti-RSV antibodies but remained culture negative. Her cerebrospinal fluid culture for RSV was negative. A 3-day course of inhaled ribavirin followed by a 6-day course of iv ribavirin was administered. Eventual marrow recovery was accompanied by a slow but steady resolution of all her RSV related symptoms as well as the clearance of her respiratory RSV. Thereafter, she has remained RSV negative. Currently she remains well in remission on ongoing ALL chemotherapy 8 months after the RSV episode.

DISCUSSION

Our experience further supports the role of RSV as a potential cause of serious morbidity among pediatric patients markedly immunosuppressed through the use of anticancer chemotherapy. Whereas BMT patients, particularly prior to engraftment, seem to be at the highest risk of serious RSV related morbidity [1,3,4], our experience leaves the role of marrow recovery in the eventual clearance of RSV unresolved. The clearance of RSV may be preceded by marrow recovery or viral marrow suppression needs to be eliminated prior to marrow recovery.

Although three-quarters of our patients who received inhaled and two-thirds of those who received iv ribavirin recovered, the role of ribavirin in the treatment of symptomatic RSV infections among children with cancer remains to be established. However, our experience indicates that promptly administered ribavirin may be beneficial in slowing or even terminating the progress of the infection in severely neutro/lymphopenic patients prior to marrow recovery.

With no RSV relapses, our data suggest that the risk of a relapse with recurrent granulo/lymphopenia may well be smaller than previously reported [2].

As to the diagnosis of RSV infections among children on anticancer chemotherapy, we found nasopharyngeal antigen detection through immunofluorescence both rapid and reliable. In contrast, the cultivation of RSV from the upper airways is difficult, and most of these children appear unable to mount an adequate antibody response against RSV. Additionally, both of these techniques introduce an unnecessary diagnostic delay even when successful.

Based on their lack of upper respiratory tract symptoms upon admission, we think that at least half of our patients probably had a nosocomially acquired infection. Consequently, in agreement with the experience of Hall and co-workers [2], we emphasize the importance of isolationary measures in the prevention of the spread of RSV within a hematology-oncology unit.

In order to treat the ones infected successfully as well as to limit the spread of RSV among children receiving anticancer chemotherapy, the pediatric oncologist has to be aware of the epidemiology of RSV in the population. During an epidemic we recommend at least the small as well as the preschool-age patients of the unit with even mild upper respiratory symptoms to be screened for RSV.

Finally, as to the prevention of RSV infection among pediatric patients, data are available on the successful use of RSV immune globulin among infants at high risk for a serious RSV infection [8]. Data on its use among children with cancer are, however, currently unavailable.

In conclusion, our experience points out that the risk for serious RSV-related morbidity among pediatric oncologic patients should not be underestimated. Yet among children receiving nonmyeloablative chemotherapy, despite considerable RSV-related morbidity, mortality is low when a combination of focused and supportive therapy is administered.

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